REMARKS

Prior to entry of the claim amendments presented above, claims 1-23 were pending in the application and stood rejected. In the present amendment, claims 1-23 have been canceled and claims 24-51 have been added. Accordingly, claims 24-51 are now pending. The cancellation of claims is made herein without prejudice or disclaimer of the subject matter recited therein, and applicants expressly reserve all rights to such subject matter.

Objection to the Specification

Applicants traverse the objection to the specification, noting the that the format suggested by the Examiner is merely a "guideline" that is "suggested" in the MPEP for applicants' use. The proposed format is not required by statute or PTO rules. Accordingly, applicants submit that amendment is not necessary as the present specification already is understandable to the skilled artisan and conforms to all formality requirements of the PTO rules.

Title of the Invention

Applicants have changed the title of the invention to "Method of Filtering Viruses From a Factor VIII Solution," thereby rendering this objection moot.

Abstract

Applicants have presented an abstract.

Trademarks

Applicants have capitalized the trademark Planova and amended the specification to include its generic terminology. Support for the generic terminology added to the specification is found in the manufacturer's catalogue, attached as Exhibit 1.

Rejections Under 35 USC §112, First Paragraph

Claim 1 is rejected under 35 USC § 112, second paragraph, for lack of enablement. Applicants respectfully traverse the rejection and new claim 24 renders this rejection moot.

New claim 24 positively recites "obtaining a starting factor VIII solution devoid of factor VIII-vWF complexes" thereby rendering this rejection moot.

Rejections Under 35 USC §112, Second Paragraph

Claims 1-23 are rejected under 35 USC § 112, second paragraph, for being indefinite. New claims 24-51 have been amended to correct multiple dependency and have been rephrased to read more clearly and conform to standard US practice to overcome this rejection.

Relative Terms

The Examiner has rejected all relative terminology in the claims. Applicants traverse this rejection and urge that all releative terminology present in the amended claims would be understood by one of ordinary skill in the art. As stated in Section 2173.05(b) of the MPEP, "[T]he fact that claim language, including terms of degree, may not be precise, does not automatically render the claim indefinite under 35 U.S.C. 112, second paragraph." (Citing *Seattle Box Co., v. Industrial Crating & Packing, Inc.*, 731 F.2d 818, 221 USPQ 568 (Fed. Cir. 1984)).

Essentially (claim 24)

Applicants note that the MPEP summarizes *In re Marsoi*, where the Federal Circuit held that the phrase "a silicon dioxide source that is essentially free of alkali metal" was definite because of the guidelines and examples of the specification and it would be impractical to require applicants to provide a specific cutoff number. (See MPEP Section 2173.05(b), citing *In re Marsoi*, 710 F.2d 799, 218 USPQ 289 (CCPA)). Similar to this case, applicants have provided guidance through the specification and examples, including Example 6, as to the phrases "essentially free of viruses" and "essentially devoid of vWF and factor VIII-vWF complexes." Moreover, applicants submit that this phrase would be well understood by one of ordinary skill in the art.

Lower Than (claims 32-34)

Applicants contend that a threshold "lower than one recommended by the supplier" would be understood by one skilled in the art. For a certain filtration device, an artisan would

merely have to read the manufacturer's instructions, and use a pressure lower than what the manufacturer recommends. Likewise in the case of "lower than" "0.3 bar" or "0.2 bar," the artisan would merely have to adjust the pressure of the filtration device so that it was lower than the recited amount.

At Least Equal to (claims 44 and 45)

Applicants contend that "at least equal to" as it appears in claims 44 and 43 is definite. One skilled in the art would understand that the meaning is a solution, having the recited activity, in the recited amounts or higher.

Approximately (claim 46-49)

The use of the term "approximately" is analogous to the term "about," which has been found to be "clear, but flexible." (See MPEP Section 2173.05(b), citing *Ex parte Eastwood*, 163 USPQ 316 (Bd. App.; 1968), and *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983)). Applicants submit that the ranges of "approximately 10 to approximately 50 U/ml," "approximately 0.05 to approximately 0.5 mg/ml," and "approximately 0.1 to approximately 0.5 mg/ml," would be understood by one of skill in the art.

Salt Saturation

Applicants contend that the term "to salt saturation" would be understood by the skilled artisan to be the concentration point of an added salt at which saturation occurs. An introductory chemistry book would define saturation as the point where a dissloved solution is in equilibrium with respect to a given dissolved substance. Saturation would depend in part on the solution, the salt and the temperature, and would be clearly understood by one of skill in the art.

Rejections Under 35 USC §103(a)

Claims 1-23 are rejected under 35 USC § 103(a) as being unpatentable over WO 96/00237 taken with Josic et al. (J. Chromatogr. B. Biomed Appl., Vol. 662, No. 2, pp. 181-190, 1994), Grandgeorge et al (U.S. Patent No. 5,371,195) and Farb et al (U.S. Patent No. 4,758,657). Applicants respectfully traverse the rejection. In the attached manufacturer's

catalogue, Factor VIII, which has a molecular with of about 300 kd, is shown as not being able to pass through the Planova 15N filter. In theory, only molecules having a molecular weight below 160 kd can pass through a 15 nm filter. Surprisingly, the inventors have found that factor VIII is able to pass through this filter most likely because of its shape and flexibility. Accordingly, the process of the present invention not only purifies factor VIII from other plasma proteins but also filters viruses because viruses cannot pass through the 15 nm filter. This is an unexpected result, not taught or suggested by the prior art.

CONCLUSION

In view of the above remarks and amendments, it is respectfully submitted that this application is in condition for allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to telephone the undersigned at the number listed below if the Examiner believes such would be helpful in advancing the application to issue.

If any additional extension(s) of time are required for the filing of this paper, applicants expressly petition for such extension(s) and authorize the Commissioner to charge any deficiency to Deposit Account 19-0741.

Respectfully submitted,

May 20, 2002
Date

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Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 19-0741 for any such fees; and applicant(s) hereby petition for any needed extension of time.

Marked Up Version of the Specification

Marked up version of paragraph 7, lines 34-37, page 5 is below:

Among the virus filters available on the market or under development, mention may be made of, for example, the [~~Planova~~] PLANOVA® 15N membrane sold by the company Asahi Chemical Industry. PLANOVA® 15N is a fiberous filter having a mean pore size of 15 ± 2 nm.- -

Marked up version of paragraph 3, lines 29-38, page 10 though paragraph 1, lines 1-9, page 11 is below:

1260 ml of a solution which is stable at +4°C are extemporaneously reheated to +35°C to undergo a step of virus removal by filtration using a BMM [~~Planova~~] PLANOVA® 15N filter having a 15-nanometer porosity threshold and a surface area of 0.12 m^2. During the filtration, the flow rate is maintained in such a way that the transmembrane pressure is always lower than 0.2 bar. After filtration of the factor VIII, 210 ml of buffered saline solution of osmolality 1300 mOsm/kg are then filtered through the membrane to recover 1470 ml of factor VIII solution free of pathogenic viruses. The buffer solution makes it possible to equilibrate the filters for osmolality and pH, and is used to rinse the filters after filtration of the factor VIII. The factor VIII solution obtained is impoverished in von Willebrand factor of a very high degree of polymerization (≥ 15), but contains sufficient von Willebrand factor of a degree of polymerization ≥ 5 and ≥ 10 to recomplex the factor VIII after dialysis.

Marked up version of paragraph 3, lines 20-25, page 11 though paragraph 1, lines 1-5, page 12 is below:

EXAMPLE 2: The conditions are identical to those of Example 1 except that 10,000 g of cryoprecipitate, representing 1330 liters of plasma, are used. 13,700 ml of factor VIII solution virus-inactivated with respect to envelope viruses are filtered. After filtration of the factor VIII, 2 liters of buffer solution, of osmolality 1300 mOsm/kg are filtered to recover 15,700 ml of factor VIII solution free of pathogenic viruses. The

filtration membrane used is a BMM [~~Planova~~] PLANOVA® 15N membrane with a surface area of 1.0 m^2.

Marked up version of paragraph 2, lines 6-12, page 12 is below:

Table 2 reproduced below indicates, for a filtration of an equivalent 1330 liters of plasma through BMM [~~Planova~~] PLANOVA® 15N membrane with a surface area of 1.0 m^2, the amounts of factor VIII obtained at the various steps of the filtration method, as well as the specific activity and the yield from the step in question.- -

Marked up version of paragraph 4, lines 13-16, page 14 is below:

Example 4: Variation of the filterability of a factor VIII solution through a [~~Planova~~] PLANOVA® 15 N membrane as a function of the nature and of the concentration of the salts used for the dissociation.

Marked up version of paragraph 3, lines 13-15, page 15 is below:

Example 5: Variation of the filterability of a factor VIII solution through a [~~Planova~~] PLANOVA® 15 N membrane as a function of temperature and pressure parameters.- -

(1)

SPECIFICATION OF PLANOVA

PLANOVA consists of BMM (Bemberg Microporous Membrane) hollow fibers, a plastic housing, caps and a sealant.

Specification	Model	PLANOVA 15N	PLANOVA 35N	PLANOVA 75N
Mean pore size (nm)*1		15 ± 2	35 ± 2	72 ± 4
Materials*2	Hollow fiber membrane	Cuprammonium regenerated cellulose		
	Housing	Polycarbonate		
	Sealant	Polyurethane		
Effective surface area of membrane (m²)		0.001		0.001
		0.01		0.01
		0.12		—
		0.3		0.3
		1.0		1.0
Sterilization method		Autoclave (121°C×within 120 min)		
State of filter		Filled with purified water		

*1 Mean pore size is determined by the water flow rate method.

*2 Data relating to safety aspects are available.

*3 PLANOVA filters are packed separately in a sterilizing package.

PLANOVA 75N is effective as a prefilter for solutions which include a variety of particle impurities.

PLANOVA®
Asahi KASEI

SUCCESSFUL PERFORMANCE OF THE NEW VIRUS REMOVAL FILTER PLANOVA 20N

B. Metzig[1], S. Satoh[2], T. Sato[1]; 1 Asahi Kasei Deutschland GmbH/D, 2 Asahi Kasei Corporation/J

Introduction

Nanofiltration using Planova filters during the purification of plasma-derived and biopharmaceutical proteins has gained strong esteem as the validatable, robust method leading to a highly purified product with a preserved biological function and a large degree of virus and prion safety (1). Nevertheless until now it was still difficult to achieve a good permeability of large proteins like Factor VIII and plasma-derived immunoglobulines while retaining the ability to remove small non-enveloped viruses like parvo virus and hepatitis A virus. In particular, these small non-enveloped viruses are extremely resistant against other well established inactivation methods. Consequently, authorities are concerned about the risk that contaminated parenterals could infect patients and request that all production processes should contain effective validated steps for the inactivation/removal of wide-range of viruses including enveloped and non-enveloped viruses (2). Therefore Asahi Kasei developed the new membrane Planova 20N. The following studies demonstrate the excellent filtration performance of Planova 20N, matching the manufactures demands of good flow rates and a high protein recovery. In addition, different viruses of diverse physico-chemical characteristics are removed. Figure 1 schematically shows an overview of different viruses, immunoglobulines and Planova® filters including Planova 20N (3, modified).

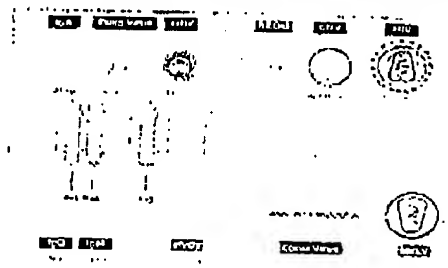

Figure 1

Material and Methods

Conditions of Nanofiltration

- Dead-end flow mode
- Single/double filtration
- Planova 20N (0.001m², 0.01 m²)
- Constant pressure 0,8 bar

A Protein filtration: Different protein solutions (Table 1). IgG solutions pre-filtered with Planova 35N, Factor VIII with Planova 75N.

B Virus filtration: DMEM + 5% FBS (or Horse Serum) spiked with different viruses (Table 2). Pre-filtration with Planova 35N: Polio Virus, PPV; Planova 75N: SV 40, BVDV.

Membrane Structure

The materials to assemble Planova 20N are the same as those of Planova 15N and Planova 35N. On the contrary, the number of active layers is increased whereas the pore size of Planova 20N is slightly larger than that of Planova 15N (Figure 2). The robustness of performances is attributed to the three-dimensional networked membrane pore structure of capillaries and voids.

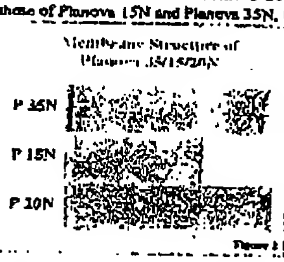

Figure 2

Filtration Mechanism

Planova® filters consist of hollow fibers which comprise approximately 150 layers of regenerated cellulose.

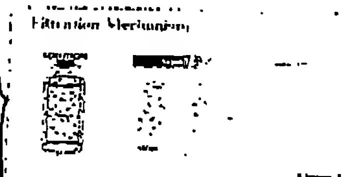

Figure 3

Thus, the filtration is based on two mechanisms:

- depth filtration
- size exclusion

While normal proteins pass readily through this hydrophilic structure, infectious particles like viruses are removed from the purification stream (Figure 3).

Results

The filtration performance of Planova 20N using different products is summarised in table 1. Human plasma-derived IgG was filtered in concentrations of 1% and 3% resulting into filtration rates of 13,5-18,7 l/m²/h and 5,0-9,3 l/m²/h and a protein recovery of 100% and >95%, respectively. Factor VIII solution gave rise to a filtration performance of 17,0-35,0 l/m²/h and a yield of 96%. Figure 4 exemplary depicts for the case of 3% human IgG that the filtration rate kept constant during a time of 7 hours at about 6,5 l/m²/h. The data shown are mean values of three different runs.

Protein Filtration Performance

Product	Filtration Rate (l/m²/h)	Recovery (%)
1% human plasma-derived IgG	[illegible]	[illegible]
3% human plasma-derived IgG	[illegible]	100
Factor VIII	[illegible]	-

Table 1

Filtration of 3% Human IgG

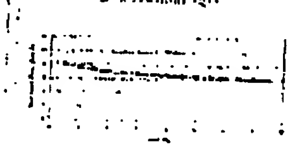

Figure 4

Effect of Double Filtration on PPV Reduction

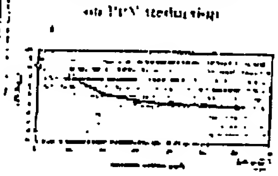

Figure 5

Virus Removal Data

Virus	Size (nm)	Envelope	Filtration	Log Reduction (LRV)
MuLV*	80-110	+	Single	[illegible]
BVDV**	50-70	+	Single	[illegible]
SV 40***	40-50	-	Single	[illegible]
Polio Virus	22-30	-	Double	8,09
Polio Virus	25-30	-	Double	[illegible]
Parvovirus	18-24	-	Single	[illegible]
PPV	18-24	-	Double	[illegible]

[illegible]

Table 2

The virus removal data of table 2 show that viruses between 40 and 110 nm, like MuLV*, BVDV** and SV 40*** are completely removed already with single filtration. The small non-enveloped viruses polio virus and porcine parvo virus (PPV) are reduced 8,09 log and 4,7 log in the case of single and >8,55 log (complete removal) and 6,6 log at double filtration. The positive effect of double filtration is clearly illustrated in figure 5. The reduction of PPV is increased about 2 logs by the employment of double filtration.

Discussion

In summary, the presented data demonstrate that the new developed membrane Planova 20N matches the demands of manufacturers by providing high flow rates which have been kept constant up to more than 7 hours and an excellent yield of >95-100% for large proteins such as human plasma-derived IgG and Factor VIII. Previous studies demonstrated that the biological function of protein is still preserved after filtration with Planova® filters (4). Furthermore it was demonstrated that Planova 20N has the capability to remove viruses as large or larger than 40-50 nm completely regardless to their physico-chemical characteristics. Even the titer of small non-enveloped viruses is reduced efficiently by single filtration. Double filtration increases the efficacy significant. Therefore manufactures have a new powerful tool to meet the requests of authorities regarding the enlargement of virus safety in their purification process.

Conclusion

The results of the presented studies demonstrate that the new developed Planova 20N is an additional powerful tool to purify plasma-derived and biopharmaceutical proteins. Planova 20N has a high potential to permeate large proteins while still being able to remove even small non-enveloped viruses to a high degree.

Acknowledgements

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Andrew M. Lockhart — BRFF, Inc., Maryland, USA
Judith Foley — BRFF, Inc., Maryland, USA

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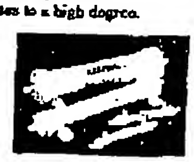
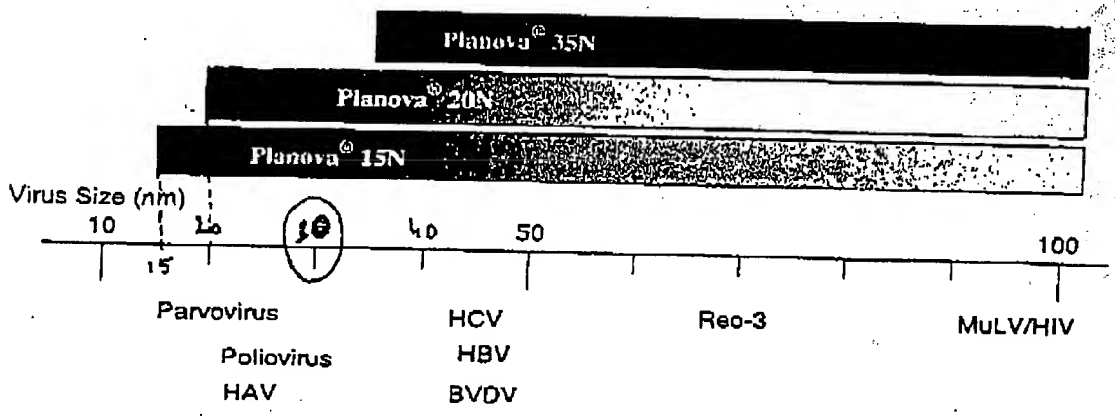


Information:
www.PlanovaFilters.com

Planova® Virus Removal Filter Product Guide

Viruses Removable by Planova® Filters



Typical Biotherapeutic Products Applied to Planova® Filters

Biotherapeutic Product	MW (kD)	Planova® 15N	Planova® 20N	Planova® 35N
Interleukin	12-33			
Interferon	20			
Thrombin	96			
Factor IX	58			
Antithrombin	65			
IgG (pepsin-treated)	~160			
Factor VIII (vWF dissociated)	300			
IgG (mAb)	160			
IgG (plasma-derived)	>160			
Factor VIII	>300	*		
Fibrinogen	340			
IgM (mAb)	900			

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